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UPS: Opportunities and challenges for gastric cancer treatment

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Gastric cancer remains the fourth most frequently diagnosed malignancy and the fifth leading cause of cancer-related mortality worldwide owning to the lack of efficient drugs and targets for therapy. Accumulating evidence indicates that UPS, which consists of E1, E2, and E3 enzymes and proteasome, plays an important role in the GC tumorigenesis. The imbalance of UPS impairs the protein homeostasis network during development of GC. Therefore, modulating these enzymes and proteasome may be a promising strategy for GC target therapy. Besides, PROTAC, a strategy using UPS to degrade the target protein, is an emerging tool for drug development. Thus far, more and more PROTAC drugs enter clinical trials for cancer therapy. Here, we will analyze the abnormal expression enzymes in UPS and summarize the E3 enzymes which can be developed in PROTAC so that it can contribute to the development of UPS modulator and PROTAC technology for GC therapy.

KEYWORDS

UPS modulator, PROTAC, E3 ligase, gastric cancer, therapy

1 Introduction

According to the global cancer statistics, one million new gastric cancer (GC) cases and about 769,000 deaths were estimated in 2020, ranking fourth for mortality and fifth for incidence among all types (1). At present, the clinical treatments of GC mainly include surgical resection, chemotherapy, radiotherapy, and molecular targeted therapy (2, 3). Molecular targeted therapy has achieved major success in recent years with the understanding of molecular mechanisms in cancer. However, only scant targets are used to develop drugs in GC such as VEGFR-2, HER2, PD-1, etc. (4). Moreover, most of traditional small molecule inhibitors affect active site of the targets to inhibit its function.

Abbreviations: GC, gastric cancer; PROTAC, proteolysis-targeting chimeras; UPS, ubiquitin-proteasome system

Due to the limit of drugs targets and related technology, the development of targeted therapy for GC is still limited. Thus, investigating more effective therapeutic targets and developing novel technologies for GC treatment are highly expected. Ubiquitin-proteasome system (UPS) is one of the main pathways for protein degradation in mammals, which regulate various cellular biological processes through changing the protein levels, such as cell signal transduction, cell cycle, transcription, DNA damage and repair, etc. (5, 6). Through the coordination between ubiquitin-activating enzyme E1, ubiquitin-conjugating enzyme E2 and ubiquitin-ligase E3 in UPS, target proteins modified by ubiquitin are transferred to the proteasome for degradation. Therefore, UPS is essential for maintaining the normal levels of intracellular proteins by removing damaged organelles and misfolded proteins (7). During GC development, it is commonly observed that dysfunction of UPS due to the abnormal changes of E1, E2, and E3 enzymes causes the imbalanced accumulation of large numbers of proteins. Fortunately, it has been validated by clinical success of many UPS modulators, emphasizing the therapeutic potential of this pathway (8). Besides, PROTAC (proteolysis-targeting chimeras) is the novel drug development technology using UPS to degrade target proteins, which plays an important role in the treatment of prostate cancer and breast cancer (9). Hence, to develop targeted drugs by using UPS has bright prospects for further GC treatment. This review will elaborate the research progresses of UPS modulators and PROTAC to provide a novel perspective for targeted therapy of GC.

2 UPS is a viable strategy in GC therapy

Compared with other cancers, such as breast cancer (HER2) and lung cancer (EGFR, ALK, ROS1), there are still no effective molecular targets for GC which lacks the dominant driver genes and epigenetics targets. Thus, researchers are turning their attention to other fields. UPS, as an important system for degradation of intracellular proteins, has attracted more attention for GC treatment. Accumulating evidence indicates that abnormal expression of E1, E2, and E3 enzymes is involved in the GC tumorigenesis, resulting in imbalance of intracellular protein homeostasis. UBE2C, UBE2T, UbcH10 are significantly upregulated in GC, which correlate with poor differentiation, high T classification, and poor prognosis (10–12). A fraction of E3 enzymes, such as MDM2, MKRN1, Cullin1, and Hakai, are overexpressed and have established oncogenic roles in gastric carcinogenesis (13–16). Numerous E3 enzymes, including FBXW7 and CHIP, have been shown to function as typical tumor suppressors in GC owing to frequent inactivating mutations or downregulated expression in GC (17). Besides, the proteasome is the primary site for protein degradation, and its activity affects UPS efficiency (18). Mechanically, abnormal UPS could lead to gastric cancer by regulating the epithelial-mesenchymal transition (EMT) through degradation of E-cadherin and N-cadherin, affecting the cell cycle through regulation of cell cycle proteins p21/p27 and cyclin D, impacting apoptosis by regulating the expression of BAX and Bcl-2 proteins. Furthermore, abnormal UPS influences the PI3K/AKT, Hippo pathway, p53 pathway, TGF-β signaling, STAT3 signaling, Wnt/β-catenin pathway, NF-κB pathway, autophagy, and so on by regulation of corresponding protein in these signaling pathway such as p53, β-catenin, SHP-1, etc. (Figure 1). Consequently, UPS can be considered as promising targets and it is a worth strategy by modulating the abnormality of UPS during the progression of GC for developing therapeutic drugs.

3 UPS modulators

UPS is a complex structure involving the proteasome; and the E1, E2, and E3 enzymes (19). Derangements of UPS leads to alterations in protein homeostasis and causes many human diseases, particularly cancer (20). Here, the recent advances of

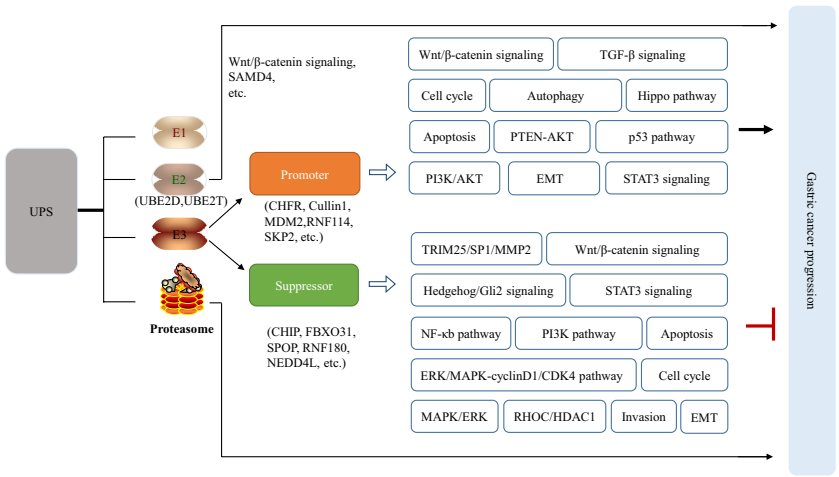

FIGURE 1
Abnormal UPS affects the normal signaling pathways in cells, leading to or inhibiting the occurrence of gastric cancer.

UPS modulators by targeting proteasome and enzymes and how they pave the way towards GC treatment are discussed in detail below (with the working model seen in Figure 2).

3.1 Targeting proteasome for GC

The proteasome is a large multi-protein complex designed to degrade proteins specifically marked by ubiquitination (21). In 2003, the FDA approved bortezomib as the first proteasome inhibitor for treating multiple myeloma that hugely increase the survival time of patients with multiple myeloma, which has provided ample evidence that targeting the proteasome is a viable approach for the treatment of human cancer (22, 23). For GC, bortezomib suppresses proliferation *in vitro* and *in vivo*, and is more effective in GC cells with lower NF-κB activation than others (24). In addition, proteasome inhibitor MG132 can effectively reverse the multidrug resistance by promoting drug-induced apoptosis of GC cells and inhibiting the expression of p-glycoprotein, confirming the hypothesis that proteasome inhibitors may be effective chemotherapeutics for GC with multidrug resistance (25). Unfortunately, the results of the phase II clinical trial show that bortezomib as a single inhibitor is inactive in advanced or metastatic GC therapy (26, 27). Therefore, future studies of proteasome inhibitor should focus on the combination of other targeted drugs in GC therapy.

3.2 Targeting E1 and E2 enzymes for GC

Ubiquitin-activating enzyme E1 is the first enzyme in UPS, which mediates the activation of ubiquitin. In mammals, only two E1 enzymes including UAE and UBA6 have been discovered (28). At present, a variety of E1 enzyme inhibitors have been reported, such as PYZD-4409 and TAK-243 that inhibit the activity of UAE. PYZD-4409 not only inhibits the growth of primary acute myeloid leukemia cells *in vitro*, but also delays tumor growth in mouse models of leukemia *in vivo* (29). In addition, TAK-243, as a new class of drugs inhibiting UAE, can induce the death of various cancer cells and attenuate the growth of xenograft models of many types of tumors (8). To date, however, there is no report on E1 enzyme inhibitors for GC due to the low specificity of inhibitors and less E1 enzymes.

Ubiquitin-conjugating enzyme E2 as the key enzyme performs the second step of the ubiquitination reaction (30). The human genome encodes around 40 different E2 enzymes (31). Accumulating evidence suggests that E2 enzymes are crucial in the occurrence and development of cancer (32). Based on the indispensability and diversity of E2 enzymes in ubiquitination, more and more inhibitors are designed for E2 than E1 enzymes. For example, the silence of UBE2D1 reduces the ubiquitination of SMAD4, inhibiting the migration of GC cells (33). Moreover, UbcH10 promotes the growth of GC cells and may represent a potential biomarker for GC (12). Besides, the novel UBE2T inhibitor controls the overactivation of Wnt/β-catenin signaling and the progression of GC by blocking RACK1 ubiquitination (34). Thus, it is attractive to develop inhibitors targeting E2 enzymes such as UBED1, UbcH10, and UBE2T for GC treatment.

3.3 Targeting E3 enzyme for GC

In the series of enzymatic cascades, ubiquitin-ligase enzyme E3 determines the specific recognition of target proteins and plays a key role in the functioning of the UPS (35). Compared to efforts against the E1 and E2 enzymes or proteasome, it is considered a better therapeutic target through targeting E3 enzymes for GC drug development because the E3 enzymes confer substrate specificity. Up to now, more than 600 types of E3 enzymes have been discovered in humans (36). In accordance with the roles, E3 ubiquitin ligases can be divided into two categories: tumor promoter and tumor suppressor based on their target proteins.

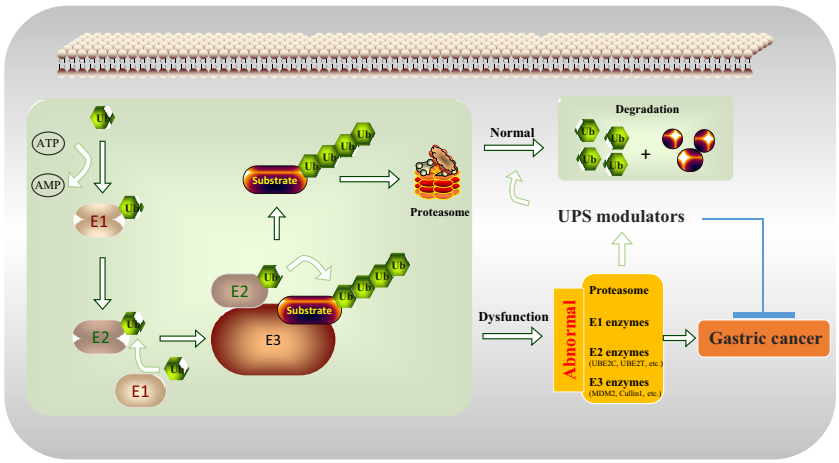

FIGURE 2
UPS modulators inhibit gastric tumorigenesis by regulating the abnormal components of the UPS including proteasome, E1 enzymes, E2 enzymes (UBE2C, UBE2T, etc.), and E3 enzymes (MDM2, Cullin1, etc.).

Although many types of E3 enzymes are reported, the related research is rare in GC development. At present, about 66 kinds of E3 enzymes are involved in GC, of which 40 types exerted an oncogenic function for promoting cancer progression and 26 types play tumor-suppressive functions (Tables 1, 2). Subsequently, representative E3 enzymes that play key roles in the development of GC will be summarized separately and analyzed the possibility as the drug targets.

The growth and development of GC can be inhibited by suppressing E3 enzymes which are the tumor promoting factor. The upregulation of MDM2 and the accompanying inactivation of p53 pathway play an important role in diffuse gastric cancer (119). MiR-410 inhibits gastric cancer cells proliferation, migration, and invasion by targeting the *MDM2* gene (120). Nutlin-3, which is the MDM2 inhibitor, has anti-tumor effects in GC cells *in vitro* and *in vivo* (121). Besides, SKP2, also named FBXL1, is an F-box typed E3 ligase, which is an overexpressed and modulated malignant phenotype *via* p27 proteolysis in GC (122). Downregulation of SKP2 inhibits the growth and metastasis of GC cells (123). Moreover, UHRF1 (Ubiquitin-Like PHD And RING Finger Domain-Containing Protein 1) expression is significantly higher in GC and is an independent and significant predictor of GC prognosis (124, 125). The knockdown of UHRF1 suppresses the growth, migration, invasion, and apoptosis of GC cells *via* an ROS-associated pathway (72). To date, there is no E3 enzyme inhibitor for clinical trials in GC treatment. However, the above studies show that the development of drugs that target the promoting function of E3 enzymes is valuable for GC therapy, though researching and finding the antagonist to inhibit promoter maybe the promising therapy for GC.

Different from a tumor promoter, the expression of a tumor suppressor needs to be enhanced to inhibit the occurrence of GC. RNF43 acts as a negative regulator of the Wnt signaling pathway by mediating the ubiquitination, endocytosis, and subsequent degradation of Wnt receptor complex component Frizzled. Research shows that RNF43 that inhibits cell proliferation is significantly downregulated in the gastric carcinoma, and its expression is positively correlated with p53 and negatively correlated with Ki67 and Lgr5 protein (107). RNF43 is related to the development of GC and attenuates the stemness of GC stem-like cells through the Wnt-β/catenin signaling pathway (108). The loss of endogenous RNF43 function enhances the growth of GC (126). FBXW7 is another important E3 ligase which negatively regulates GC progression. Low levels of FBXW7 protein in primary GC contributes to malignant potential and poor prognosis (127). *In vitro* studies found that FBXW7 inhibits GC progression by inducing apoptosis and growth arrest (94). In addition, CHIP is the ubiquitin ligase which contains a tetratricopeptide repeat and a U-box, and can significantly reduce the migration and invasion of GC cells though inhibiting the NF-κB signaling pathway (84). CHIP overexpression impedes the growth of xenografts in nude mice and inhibits endothelial cell growth and tube formation (128). Based on current research, enhancing the function of E3 enzymes can inhibit the development of GC. For example, eprenetapopt, as the first targeting drug of p53 as suppressor gene, binding the cysteine residue of mutant p53 and converting to the wild-type conformation, can restore p53 function. Therefore, by restoring the function of the inactivated mutant E3 enzymes to exert tumor suppressor roles, it is an interesting research field for GC treatment.

4 PROTAC

Traditional small molecule drugs and antibodies play a critical role for diseases treatment by activating or inhibiting the function of the target protein, which is defined as "occupation-driven" mode (129). This mode requires higher concentration of inhibitors or monoclonal antibodies to occupy the activity site of the target so that the transduction of downstream signaling pathways is blocked (130, 131). As an emerging new technology, PROTAC is different from the "occupation-driven" mode through the UPS system to ubiquitinate and degrade the target proteins (132–134). A PROTAC includes three key parts: E3 ubiquitin ligase ligand, POI (protein of interest) ligand, and linker (135, 136). As shown in Figure 3, in this technology, the specific target protein is recognized by the POI ligand, and the E3 ubiquitin ligase ligand is used to recruit the specific E3 enzyme of the target protein, so that the target protein and its E3 enzyme are spatially bound together *via* a flexible chemical linker to promote the degradation of the target protein (137–139). Based on this principle, a variety of PROTAC drugs have been designed and synthesized. For example, ARV-110 is the first oral bioavailable PROTAC small molecule drug that enters clinical trials in the field of PROTAC in world, which can selectively target degradation androgen receptor (AR) to treat prostate cancer (132). In the GC process, there is an abnormal expression of protein. It is attractive by looking for E3 enzymes of these proteins to design effective PROTAC drugs for GC therapy.

4.1 Advantages and disadvantages of PROTAC technology

PROTAC as the novel therapeutic technology offers numerous advantages over traditional inhibition strategies (140, 141). Firstly, the dose of traditional small molecules drugs is high, which may result in toxic side effects (142). However, in PROTAC technology, by catalyzing the degradation of the target protein, lower drug concentration could achieve good degradation efficiency to overcome on-target drug toxicity (143, 144). Secondly, the UPS is the main protein degradation system and E3 ubiquitin ligases are widely expressed in a variety of cells (145). The PROTAC molecule only needs to connect the target protein and E3 enzymes together; subsequently, protein is degraded through the proteasome (146). Therefore, PROTAC technologies have broad applications for different targets. Thirdly, PROTAC degrades the protein to the basal level within a few minutes (137). However, the re-synthesis

rate of most proteins is very slow so that the cell still needs the time to restore the physiological protein level; even PROTAC is completely cleared, thereby PROTAC could prolong the action time (147).

In general, the use of PROTAC drugs is associated with several disadvantages, such as worse membrane permeability and bad oral availability (148). In addition, the molecular weight of PROTAC is higher compared with traditional small molecule drugs because of

TABLE 1 E3 enzymes as the promoter in GC.

Types	E3 enzymes	Function	Substrate	Signal	References
RINGs	CHFR	promoter	PARP-1	EMT, Cell cycle	(37, 38)
	Cullin1	promoter	–	Cell cycle, Apoptosis	(39)
	FBXL7	promoter	Survivin	Apoptosis	(40)
	FBXO11	promoter	–	PI3K/AKT, EMT	(41)
	FBXO2	promoter	–	EMT	(42)
	FBXO6	promoter	–	Apoptosis, Invasion	(43)
	FBXW5	promoter	–	Hippo pathway	(44)
	MDM2	promoter	p53	p53 pathway	(13)
	MKRN1	promoter	p14ARF	Senescence	(14)
	PRAJA	promoter	ELF/Smad3	TGF-β signaling	(45)
	RFWD3	promoter	p53	AKT, ERK/P38 and Slug pathways	(46)
	RNF114	promoter	–	Cell cycle	(47)
	RNF115	promoter	–	Autophagy	(48)
	RNF126	promoter	–	Cell cycle	(49)
	RNF185	promoter	JWA	Metastasis	(50)
	RNF2	promoter	–	Cell cycle	(51, 52)
	RNF31	promoter	FOXP3	Metastasis	(53)
	RNF38	promoter	SHP-1	STAT3 signaling	(54)
	RNF6	promoter	SHP-1	STAT3 signaling	(39, 55)
	SIAH1	promoter	β-catenin	Nuclear translocation of β-catenin	(56)
	SIAH2	promoter	–	Invasion	(57)
	SKP2	promoter	-	Cell cycle	(58)
	TRIM14	promoter	-	AKT signaling	(59)
	TRIM15	promoter	-	Invasion	(60)
	TRIM23	promoter	-	–	(61)
	TRIM24	promoter	-	Wnt/β-catenin	(62)
	TRIM29	promoter	-	Wnt/β-catenin	(63)
	TRIM32	promoter	–	Wnt/β-catenin, AKT	(64, 65)
	TRIM37	promoter	–	NF-κB pathway	(66)
	TRIM44	promoter	–	Metastasis	(67)
	TRIM59	promoter	p53	p53 pathway	(68)
	UBR2	promoter	–	Wnt/β-catenin	(69)
	UBR5	promoter	GKN1	–	(70, 71)
	UHRF1	promoter	–	Invasion	(72)
HECTs	HUWE1	promoter	TGFBR2	Invasion	(73)

(Continued)

TABLE 1 Continued

Types	E3 enzymes	Function	Substrate	Signal	References
	NEDD4-1	promoter	PTEN	PTEN pathway	(74)
	SMURF1	promoter	MEKK2	MEK1/2-ERK1/2	(75, 76)
	UBE3C	promoter	AXIN1	Wnt/β-catenin	(77)
	WWP1	promoter	–	PTEN-Akt	(78, 79)
	WWP2	promoter	PTEN	PTEN pathway	(80)

its triplet form; as a result, its solubility may be poor (140). Besides, the production of PROTAC is more difficult and costly and the potential toxicity of PROTAC is longer than traditional small molecule drugs (149). Hence, the researchers need still pay attention to solve these problems for PROTAC drug development.

4.2 PROTAC technology in GC treatment

With GC as heterogeneous cancer, is difficult to design effective drugs using traditional targets. Patients are prone to drug resistance in the current molecular targeted drug treatment. However,

TABLE 2 E3 enzymes as the suppressor in GC.

Types	E3 enzymes	Function	Substrate	Signal	References
RINGs	CBLB	suppressor	–	Cell adhesion and Detachment	(81–83)
	CHIP	suppressor	TRAF2	NF-κB pathway	(84, 85)
	COP1	suppressor	c-Jun/p53	Invasion	(86)
	DTX1	suppressor	c-FLIP	Apoptosis	(87)
	FBX8	suppressor	–	Metastasis	(88)
	FBXL2	suppressor	FoxM1	Cell cycle	(89)
	FBXL5	suppressor	Cortactin	Invasion	(90, 91)
	FBXO21	suppressor	Nr2f2	EMT	(92)
	FBXO31	suppressor	SNAI1	EMT	(93)
	FBXW7	suppressor	MCL1/RhoA/ENO1/GFI1	Apoptosis, AKT, GSK3β	(94–97)
	MARCH8	suppressor	DR4	PI3K Pathway	(98)
	MKRN2	suppressor	PKM2	MAPK/ERK	(99)
	PRAJA2	suppressor	KSR1	MEK-ERK	(100)
	RBX1	suppressor	PRDX2	Invasion	(101)
	RNF168	suppressor	RHOC	RHOC/HDAC1	(102)
	RNF180	suppressor	RhoC	STAT3 signaling	(103–105)
	RNF181	suppressor	–	ERK/MAPK-cyclin D1/CDK4 pathway	(106)
	RNF43	suppressor	–	Wnt/β-catenin	(107, 108)
	SPOP	suppressor	–	Hedgehog/Gli2 signaling	(109)
	TRIM15	suppressor	–	Invasion	(110)
	TRIM25	suppressor	SP1	TRIM25/SP1/MMP2	(111)
	TRIM31	suppressor	–	–	(112, 113)
	ZNRF3	suppressor	–	WNT and Hedgehog signaling	(114, 115)
HECTs	HACE1	suppressor	–	Invasion	(116)
	ITCH	suppressor	Smad7	EMT	(117)
	NEDD4L	suppressor	–	PI3K-AKT	(118)

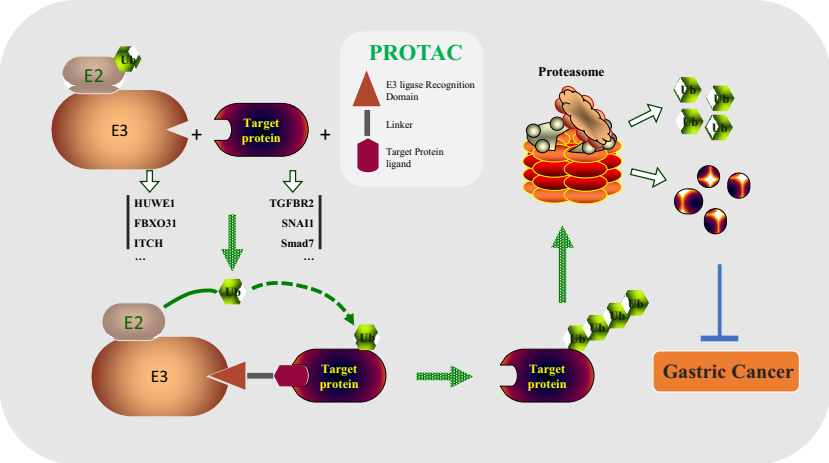

FIGURE 3
PROTAC drugs degrade important oncogenic substrates in the process of tumorigenesis by linking the E3 enzyme and substrate (HUWE1/TGFBR2, FBXO31/SNAI1, ITCH/Smad7, etc.), preventing the occurrence of gastric cancer.

PROTAC technology as a means of precise treatment could partially solve the above problems. Thus, based on the characteristics of PROTAC technology, it is a promising strategy to investigate new substrate proteins and their corresponding E3 enzyme in GC, which will provide a basis for the development of PROTAC drugs. At present, E3 enzymes are often employed for designing PROTAC including VHL, CRBN, and IAPs that belong to the RING family (9, 150, 151). Besides, cancer-related proteins such as AR, ER, BRD4, CDK4, and CDK6 are the top five studied targets for degradation (152). To date, about 10 PROTAC drugs have already entered the clinical development stages and about 110 are in pre-clinical projects worldwide. Among them, ARV-110, ARV-471, and CFT7455 that are currently the fastest clinically progressing PROTAC drugs have entered clinical phase II trials (132, 153, 154). ARV-110 is a CRBN-based PROTAC, which is designed to degrade AR for prostate cancer treatment (155). ARV-471, by degrading ER for treating breast cancer, is also a CRBN-based PROTAC (156). Moreover, CFT7455 is designed based on CRBN E3 ligases for multiple myeloma through decreasing the level of IKZF1/3 protein (157). Therefore, PROTAC technology provides the potential for development of cancer-targeted therapy drugs.

However, the development of PROTAC drugs is relatively slow in GC. According to research, ARV-825 as the PROTAC drug effectively inhibits the growth of GC cells and elevates the apoptosis through downregulation of c-MYC and PLK1, suggesting that it may be a better therapeutic strategy for GC (158), while the clinical application of ARV-825 needs to explore continually. For GC, there are more than 40 types of E3 enzymes that have been reported, but it is the focus topic how to select appropriate E3 enzymes and their targets to develop PROTAC drugs. Three main points need to be considered when choosing E3 ligase. a. Choose the E3 ligase whose main function is to induce protein degradation. b. The substrate protein of E3 enzymes should play an important role in GC development. c. The tissue and cell-level distribution of E3 enzymes should be fully considered. Here, we summarize the E3 enzymes and corresponding substrates that have been studied in GC (Tables 1, 2) so as to provide the base for the development of PROTAC drugs in the future. In addition to the selection of E3 ligase and specific target protein, it is considered to select the corresponding ligand and appropriate length linker, which is the problem that restricts PROTAC technology (159). At present, most of the ligands are the thalidomide and its derivatives to recruit CRBN in clinic (157, 160). With the development of PTOTAC, a variety of E3 enzymes including AhR, clAP1, clAP2, CRBN, DCAF11, DCAF15, DCAF16, IAP, MDM2, RNF114, RNF4, VHL, and XIAP have developed corresponding ligands (147). Besides, Linker is a structure connecting the two ligands of PROTAC drugs, the length of which have an important influence on the biological activity of PROTAC drugs (137). However, there are no general rules for linker design (161). With current challenges solved, more and more E3 enzymes that are mentioned in Tables 1 and 2 will be used to develop PROTAC drugs in the future for GC treatment. PROTAC may become another important disease treatment drug after small molecule inhibitors and monoclonal antibodies.

5 Conclusion

The occurrence and development of GC is often accompanied by the disorder of the UPS system, which is manifested as the abnormal expression of the E1, E2, and E3 enzymes. Targeting these abnormally expressed enzymes or proteasomes is a promising strategy for GC treatment. At present, these E3 ligases are worth considering as targets including MDM2, SKP2, UHRF1, RNF43,

FBXW7, and CHIP E3 enzymes widely studied in GC. However, it is easier to inhibit the function of oncogenes than to restore the roles of tumor suppressor, so E3 enzymes as oncogenes maybe more suitable. However, there are no E3 enzyme modulators for clinical trials in GC treatment to date. Considering the extensive and complex activities regulated by ubiquitination, blocking or activating E3 ligases for GC therapy may adversely affect other normal biological process. Therefore, it remains a considerable challenge to explore and solve these problems. Moreover, PROTAC is the novel technology to develop drugs for degrading intracellular important oncogenic proteins that could accomplish precise treatment of GC through the UPS. So far, only a fraction of E3 enzymes has been shown to be suitable for PROTAC. It also needs to identify more available E3 ligases and explore the mechanisms to develop PROTAC. It is believed that with the progress of basic research and clinical trials, these problems can be solved finally. Hence, targeting the Ubiquitin-proteasome system for gastric cancer is a promising strategy to supply a gap due to lack of sufficient drug selection *via* the UPS system in GC therapy. To develop targeted drugs by using UPS has bright prospects for GC treatment in further studies.

Author contributions

ZL and KL conceived and designed this review. HA collected the references. HY and JZ wrote the original manuscript and made the figures. ZL, JM and KL revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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